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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/823,712	03/30/2001	Gregor Sagner	5443	7485

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ROCHE MOLECULAR SYSTEMS INC
PATENT LAW DEPARTMENT
1145 ATLANTIC AVENUE
ALAMEDA, CA 94501

EXAMINER	
CHAKRABARTI, ARUN K	
ART UNIT	PAPER NUMBER
1634	9

DATE MAILED: 06/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/823,712	Applicant(s) SAGNER ET AL.
	Examiner Arun Chakrabarti	Art Unit 1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

DETAILED ACTION

Specification

1. Claims 1-3, 5, 6, and 8-14 are amended and new claims 15-17 have been added.

Claims 14 and 17 are objected to because the use of the trademark Sybr (R) Green 1 has been noted in this application in claim numbers 14 and 17. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. .

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-17 are rejected under 35 U.S.C. 103(a) over Wittwer et al. (PCT International Publication Number WO 97/46707) (December 11, 1997) in view of Brown et al. (U.S. Patent 6,143, 496) (November 7, 2000).

Wittwer et al teach a method for determining the efficiency of the amplification of a target nucleic acid (Abstract) comprising the steps of:

b) the target nucleic acid is amplified under defined reaction conditions and the amplification is measured in real-time (Figures 9A-9G and 11A);

c) a defined signal threshold value is set (Figure 22);

d) determining the cycle number for each dilution at which the signal threshold value is exceeded (Figure 22);

e) determining a non-linear continuously differentiable function of a logarithm of copy number of target nucleic acid used for the amplification as a function of the cycle number at which the signal threshold value is exceeded (Figure 22 and Page 58, lines 1-4 and Page 59, lines 1-15); and

f) calculating the amplification efficiency from the function determined in step e) (Page 59, lines 1-15).

Wittwer et al teach a method, wherein the amplification efficiency of a certain original amount of target nucleic acid is determined as the negative and reciprocal local first derivative of the continuously differentiable function (Page 59, lines 1-15).

Wittwer et al teach a method, wherein the non-linear continuously differentiable function is determined with the aid of polynomial fit of the third degree (Page 59, lines 1-22)

Wittwer et al also teach a method for the absolute quantification of a target nucleic acid in a sample (Abstract and Page 66, lines 16-23)) comprising the steps of:

a) determination of the amplification efficiencies of the target nucleic acid and of an internal or external standard (Figures 22, 45 and 46);

b) amplification of the target nucleic acid contained in the sample and of the standard under the same defined reaction conditions (Figures 22, 45 and 46);

c) measurement of the amplification of the target nucleic acid and standard in real time (Figures 22, 45 and 46);

d) calculation of the original copy number in the sample with the aid of amplification efficiencies determined in step a) (Page 59, lines 1-22).

Wittwer et al. also teach a method, wherein the amplified nucleic acids are detected with the aid of at least one fluorescent-labelled hybridization probe selected from SybreGreen I (Figures 21A-21D).

Wittwer et al. teach correction of copy number with the aid of amplification efficiencies (Figure 59).

Wittwer et al inherently teach calculating the quotients of the function values (copy number) from the target nucleic acid and reference nucleic acid for the sample to be analyzed as well as for the calibrator sample and determination of the ratio of the two quotients as a measure for the original amount of target nucleic acid contained in the sample (Figures 14, 20, 22, 29 and 57 and Page 93, line 12 to page 94, line 13).

Wittwer et al do not teach the preparation of a dilution of the target nucleic acid.

Brown et al teach the preparation of a dilution of the target nucleic acid (Abstract, Example 1, Table 1 and Figure 8);

Wittwer et al do not teach a method, wherein the amplified nucleic acids are detected with the aid of at least one fluorescent-labelled hybridization probe selected from TaqMan probes.

Brown et al teach a method, wherein the amplified nucleic acids are detected with the aid of at least one fluorescent-labelled hybridization probe selected from TaqMan probes (Column 3, lines 25-59).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the preparation of a dilution of the target nucleic acid and fluorescent-labelled hybridization probe selected from TaqMan probes of Brown et al in the method of sampling, amplifying and quantifying segment of nucleic acid of Wittwer et al. since Brown et al state, "A need also exists for performing multiple different amplification and detection reactions in parallel on a single specimen and for economizing usage

of reagents in the process (Column 4, lines 23-26)". Moreover, Wittwer et al. state, "Monitoring the fluorescence of dsDNA once per cycle with dyes is an important advance that allows a wide dynamic range of initial template concentrations to be analyzed. However, the present invention's continuous monitoring within temperature cycles allows verification of product purity, simultaneous relative quantification with a competitor, and absolute product concentration determination (Page 66, lines 16-23)". An ordinary practitioner would have been motivated to substitute and combine the preparation of a dilution of the target nucleic acid and fluorescent-labelled hybridization probe selected from TaqMan probes of Brown et al in the method of sampling, amplifying and quantifying segment of nucleic acid of Wittwer et al. in order to achieve the express advantages , as noted by Wittwer et al., of a method that allows a wide dynamic range of initial template concentrations to be analyzed and also allows verification of product purity, simultaneous relative quantification with a competitor, and absolute product concentration determination and also to achieve the express advantages , as noted by Brown et al., of a method for performing multiple different amplification and detection reactions in parallel on a single specimen and for economizing usage of reagents in the process .

Response to Amendment

4. In response to amendment, all 112 (second paragraph) rejections are hereby withdrawn. However, 103 (a) rejection is maintained.

Response to Arguments

5. Applicant's arguments filed on February 26, 2002 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant argues that there is no motivation to combine the references. This argument is not persuasive, especially in the presence of strong motivation provided by Brown et al as Brown et al. state, "A need also exists for performing multiple different amplification and detection reactions in parallel on a single specimen and for economizing usage of reagents in the process (Column 4, lines 23-26)". Moreover, Wittwer et al. state, "Monitoring the fluorescence of dsDNA once per cycle with dyes is an important advance that allows a wide dynamic range of initial template concentrations to be analyzed. However, the present invention's continuous monitoring within temperature cycles allows verification of product purity, simultaneous relative quantification with a competitor, and absolute product concentration determination (Page 66, lines 16-23)".

Applicant also argues that Wittwer reference does not teach the main feature of the instant invention which is the determination of an amplification efficiency. This argument is not persuasive. Wittwer reference clearly teaches the determination of an amplification efficiency (Figures 22, 45 and 46 and 59 and Abstract, last line).

Applicant also argues that Wittwer reference in Figure 21 D does not teach the determination of a non-linear continuously differentiable function of a logarithm of copy number of target nucleic acid used for the amplification as a function of the cycle number at which the signal threshold value is exceeded. This argument is not persuasive.

Although not specifically in Figure 21 D, Wittwer reference clearly teaches the determination of a non-linear continuously differentiable function of a logarithm of copy number of target nucleic acid used for the amplification as a function of the cycle number at which the signal threshold value is exceeded (Figure 22 and Page 58, lines 1-4 and Page 59, lines 1-15).

In view of the response to argument, all 103 (a) rejections are hereby being properly maintained.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Arun Chakrabarti

Patent Examiner

Art Unit 1634

May 22, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600